Effect of Hypothermia/Anesthesia Induced by α2-Adrenoceptor Agonist on Monoamine Turnover and Neurotensin Concentrations in the Rat Brain[a]

N. ERIC NAFTCHI,[b] HENRY SERSHEN,[c] AUDREY HASHIM,[c] AND GARTH BISSETT[d]

[b]*Laboratory of Biochemical Pharmacology*
New York University Medical Center
New York, New York 10016

[c]*The N.S. Kline Institute for Psychiatric Research*
Center for Neurochemistry
Orangeburg, New York 10962

[d]*Duke University Medical Center*
Durham, North Carolina

Treatment of 13 Sprague-Dawley rats with guanabenz (4 mg/kg), an α-adrenoceptor agonist, significantly reduced neurotensin (NT) concentrations only in the caudate nucleus. The NT content of the hypothalamus, olfactory tubercles, and nucleus accumbens was also reduced, but not at the 95% significant level; that of the frontal cortex, preoptic nucleus, septum or ventral tegmental area/substantia nigra was unchanged. Twenty minutes after treatment with guanabenz (4 mg/kg) at a room temperature of 22.5–23.0 °C, the core temperature of the treated rats (warm treated, WT) was 34.7 ± 0.4 °C and that of the control rats (warm control, WC) was 36.7 ± 0.75 °C. The core temperature of the control animals (cold control, CC) in a temperature-controlled room (3.7 °C) was 35.4 ± 0.12 °C compared with 30.8 ± 0.3 °C for guanabenz-treated animals (cold treated, CT). In the cold-control animals, 5-hydroxyindoleacetic acid (5-HIAA) increased significantly in the frontal cortex, hippocampus, and corpus striatum (TABLE 1). The concentration of 5-HT was also significantly reduced in the striatum. These results indicate that, with the exception of the hippocampus, an increase occurs in the turnover of 5-HT in the frontal cortex and the corpus striatum due to cold stress. Dopamine turnover also increased significantly in the frontal cortex and the corpus striatum. The induced changes in 5-HT and dopamine turnover by cold stress were abolished by guanabenz treatment; no significant difference was found in the striatal dopamine and 5-HT among the vehicle-treated control rats in the room ambiance (WC) and rats treated in the cold (CT) temperatures (TABLE 1). Anterior hypothalamus showed no change either due to cold or to treatment with guanabenz in any of the neurotransmitters and their metabolites (TABLE 2).

The regions of caudate nucleus and preoptic hypothalamus where NT concentra-

[a]This work was supported by Edmund A. Guggenheim, and Murray and Leonie Guggenheim Clinical Research Endowment Funds.

TABLE 1. Effect of Guanabenz on Cathecholamine Levels in the Brain

	5HIAA	5HT	DOPAC + HVA/DA	5HIAA/ 5HT
Frontal Cortex				
WC	1.95 ± 0.11	4.71 ± 0.20	0.69 ± 0.11	0.38
WT	1.58 ± 0.24	3.96 ± 0.50	1.02 ± 0.08	0.37
CC	3.13 ± 0.36[a]	4.65 ± 0.53	1.09 ± 0.11[b]	0.62[a]
CT	1.93 ± 0.13[a]	5.12 ± 0.53	0.71 ± 0.14[b]	0.35
Hippocampus				
WC	2.42 ± 0.10	2.10 ± 0.11	0.54 ± 0.12	1.06
WT	2.80 ± 0.10	2.75 ± 0.12	0.55 ± 0.13	0.94
CC	4.43 ± 0.20[a]	3.77 ± 0.99	0.59 ± 0.07	1.08
CT	3.76 ± 0.06[a]	3.88 ± 0.21	0.72 ± 0.28	0.89
Striatum				
WC	3.04 ± 0.17	3.27 ± 0.29	0.19 ± 0.01	0.86
WT	3.54 ± 0.19	4.18 ± 0.16	0.17 ± 0.01	0.78
CC	4.00 ± 0.33[b]	2.85 ± 0.27[b]	0.25 ± 0.02[a]	1.29[a]
CT	2.70 ± 0.25[a]	3.36 ± 0.53	0.17 ± 0.01[a]	0.74

NOTE: Animals killed 20 min after injection. Values are expressed as ng/mg protein, mean ± SEM, $n = 4–5$; significant comparisons are between WC versus CC and CC versus CT.
[a]$p < 0.01$ and [b]$p < 0.05$.
Legend: Warm control (WC): Saline; room temperature, 22.5–23 °C; body temperature, 36.7 ± 0.75 °C. Warm treated (WT): Guanabenz, body temperature, 34.7 ± 0.04 °C. Cold control (CC): Saline, room temperature, 3.7 °C; body temperature 35.4 ± 0.12 °C. Cold treated (CT): Guanabenz, body temperature 30.8 ± 0.3 °C.

tions were significantly altered contain intrinsic NT neurons, as well as some terminals that project from other regions.[1,2] Neurotensin is known to be colocalized with dopamine in neurons of the ventral tegmental area that project to the nucleus accumbens and frontal cortex. The lack of significant NT changes in any of these regions, however, would argue against this source of NT being affected by the treatment with guanabenz. Administration of neuroleptic drugs is known to increase NT levels[3] and NT messenger RNA concentrations[4] in the caudate nucleus and nucleus accumbens. This effect of neuroleptics is still present after destruction of dopamine neurons innervating these regions.[5] Thus, guanabenz may be decreasing NT concentrations by affecting local circuit neurons containing NT in the caudate nucleus and preoptic hypothalamus.

The results demonstrate that cold stress induces a marked increase in the turnover of 5-HT in the frontal cortex, hippocampus, and corpus striatum; there is a decrease in the [5-HT/5-HIAA] ratio. With the exception of the hippocampus, the same results also apply to dopamine turnover; the ratio of [DOPAC + HVA)/DA]

TABLE 2. Effect of Anesthesia/Hypothermia Induced by Guanabenz-Acetate on Biogenic Amine Levels in Anterior Hypothalamus[a]

	DOPAC	DA	HVA	5HT	5HIAA	NE
Control	0.65 ± 0.2	4.5 ± 1.0	0.42 ± 0.07	9.8 ± 0.9	3.9 ± 0.4	13.5 ± 2.7
Cold Control	0.65 ± 0.2	4.8 ± 1.6	0.43 ± 0.08	8.2 ± 2.0	4.1 ± 1.0	14.4 ± 3.0
Treated	0.79 ± 0.3	6.3 ± 2.0	0.55 ± 0.16	10.2 ± 1.6	2.8 ± 0.5[b]	13.8 ± 1.7

[a]Results expressed as ng/mg protein, mean ± SD.
[b]$p < 0.05$.

increased significantly in the frontal cortex and the corpus striatum (TABLE 1). Alterations in 5-HT and dopamine turnover induced by cold stress are abolished by guanabenz treatment. Guanabenz, therefore, attenuates the increase in dopamine and 5-HT turnover induced by cold stress in the brain (TABLE 1 compares results in ambient temperature, WC versus CT).

Anterior hypothalamus showed no change in any of the neurotransmitters and their metabolites either due to cold or to treatment with guanabenz (4 mg/kg). In this discrete area of the brain, including the posterior hypothalamus, a significant reduction in 5-HIAA occurred, which may be a sign of decreased activity of membrane-bound intraneuronal monoamine oxidase, but not that of extraneuronal catechol-*O*-methyl transferase in this tissue (TABLE 2).

ACKNOWLEDGMENTS

This paper is dedicated to Jude Sleis for her years of impeccable service. Her untimely departure leaves a great void.

REFERENCES

1. EMSON, P. C., M. GOEDERT & P. W. MANTYH. 1985. *In* Handbook of Chemical Neuroanatomy, Vol. 4. A. Bjorkland & T. Hokfelt, Eds.: 355–405. Elsevier. Amsterdam.
2. ZAHMS, D. S. 1987. Neurosci. Lett. **81:** 41–47.
3. KILTS, C. D., C. M. ANDERSON, G. BISSETTE, T. D. ELY & C. B. NEMEROFF. 1988. Biochem. Pharmacol. **37:** 1547–1554.
4. MERCHANT, K. M., P. R. DOBNER & D. M. DORSA. 1992. J. Neurosci. **12:** 652–663.
5. BISSETTE, G., K. DOLE, M. JOHNSON, *et al.* 1988. Soc. Neurosci. Abstr. **14:** 1211.